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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,828	02/11/2004	Robert J. Cherney	PH 7442 NP	3372

23914 7590 04/26/2006

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EXAMINER	
KOSACK, JOSEPH R	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 04/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,828	CHERNEY ET AL.	
	Examiner	Art Unit	
	Joseph Kosack	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16-19,23-26,29,37 and 38* is/are pending in the application.

4a) Of the above claim(s) *23-26,29 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,16-19 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14, 16-19, 23-26, 29, and 37-38 are pending in the instant application.

Amendments

The amendment filed on April 4, 2006 has been acknowledged and has been entered into the record.

Election/Restrictions

The Restriction Requirement made on November 15, 2005 was made final in the previous office action mailed on January 18, 2006.

Status of the Claims

The amendment filed on April 4, 2006 has cancelled claims 15, 20-22, 27-28, and 30-36 and introduced new claims 37-38. Claim 37 is a product claim and will be grouped with Group I stated in the Restriction Requirement made on November 15, 2005. Claim 38 is a method claim and has been grouped with Group II stated in the Restriction Requirement made on November 15, 2005. Claim 38 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention.

Previous Claim Objections

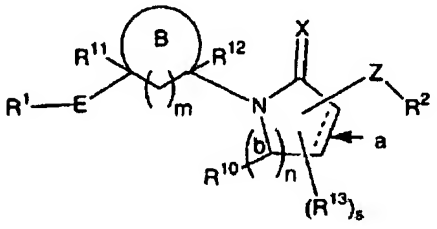
The objection to claims 1-19 made in the previous office action mailed on January 18, 2006 due to the presence of non-elected subject matter has been withdrawn since the non-elected subject matter has been removed in the amendment filed on April 4, 2006.

Response to Arguments to Claim Rejections - 35 USC § 103

Claims 1-19 were rejected in the previous office action mailed on January 18, 2006 under 35 U.S.C. 103(a) as being unpatentable over Ewing et al. (WO 99/37304 A1).

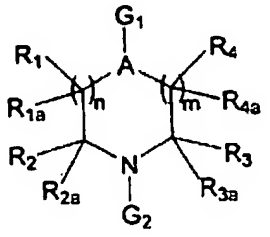
Applicant has submitted arguments contesting the rejection on the grounds that Ewing et al. does not adequately suggest the compounds of the instant invention, nor does Ewing et al. disclose the utility of the compounds as inhibitors of CCR2 and are useful in the treatment of inflammatory diseases.

The instant application cites a compound of the base structure



where: B is cyclohexyl with substitutions as defined; a is a single bond; R^1 is phenyl with substitutions as defined; n is 1; Z is -NH-; R^2 is a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted as defined; E, R^1, R^{11}, and all other substituents are as defined.

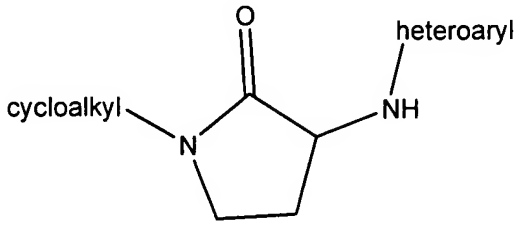
Ewing et al. teach a lactam with the base formula:



with substitutions as defined. See page 2, line 18.

When taking the definitions of the substituents in which n is 0; R_2 and R_{2a} combine to make =O or =S; G_2 is L_2-Cy_2 where L_2 is absent and Cy_2 is optionally

substituted cycloalkyl; A is CH; G_1 is L_1-Cy_1 where L_1 is NR^5 where R^5 is hydrogen and Cy^1 is optionally substituted heteroaryl; m is 1; R_3, R_{3a}, R_4, and R_{4a} are as defined.



Ewing et al. teaches cycloalkyl to be the following on page 8, lines 6-15:

"Cycloalkyl" means a non-aromatic mono- or multicyclic hydrocarbon ring system of about 3 to about 10 carbon atoms. *Representative monocyclic cycloalkyl rings include* cyclopentyl, cyclohexyl, cycloheptyl, and the like. Representative multicyclic cycloalkyl rings include decalinyl, norbornyl, adamantyl, and the like. The cycloalkyl group is optionally substituted with one or more cycloalkyl group substituents which may be the same or different, where "cycloalkyl group substituent" includes oxo, alkyl, aryl, *heteroaryl, aralkyl, heteroaralkyl, hydroxy,* hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, amidino, amino, carbamoyl, or *sulfamoyl. Preferred cycloalkyl group substituents* are amino and amidino.

Therefore, Ewing et al. adequately suggests a cyclohexyl group substituted at any position with an amino group, which is defined on page 14, lines 19-21:

"Amino" means a group of formula Y^1Y^2N- wherein Y^1 and Y^2 are defined herein. Preferred amino groups include amino (H_2N-), methylamino, dimethylamino, diethylamino, benzylamino, or phenethylamino.

Ewing et al. define Y^1 and Y^2 on page 6, lines 5-7:

Y^1 and Y^2 are independently hydrogen, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or optionally substituted heteroaralkyl, or Y^1 and Y^2 taken together with the N through which Y^1 and Y^2 are linked form a monocyclic heterocyclyl;

Ewing et al. also define aralkyl on page 13, lines 14-16:

"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as defined herein. Preferred aralkyls contain a lower alkyl moiety. Representative aralkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

Hence, Ewing et al. adequately suggest that the cyclohexyl group be substituted with an amino group such as methylamino, diethylamino, dimethylamino, benzylamino etc.

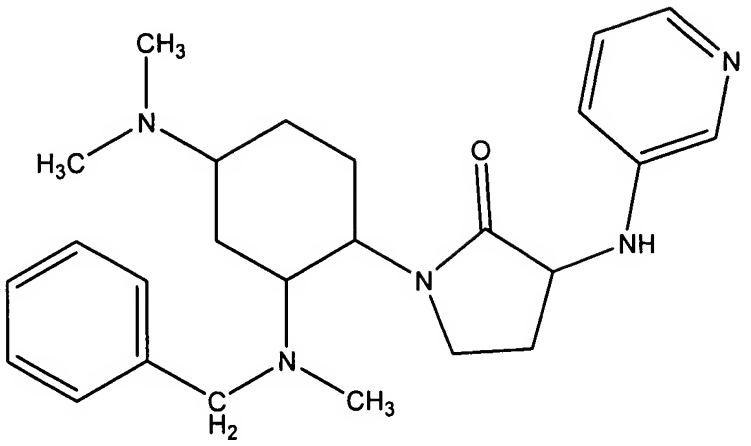
Ewing et al. define heteroaryl on page 9, line 26 through page 10, line 5:

"Heteroaryl" means about a 5- to about a 10- membered aromatic monocyclic or multicyclic ring system wherein one or more of the atoms in the ring system is/are element(s) other than carbon. Preferred heteroaryl contain one to about 4 heteroatoms selected from oxygen, nitrogen and sulfur. "Aza", "oxo" or "thia", when used as a prefix before heteroaryl means that the ring system contains at lease one nitrogen, oxygen or sulfur atom. The heteroaryl is optionally substituted with one or more aryl group substituents as defined herein. Representative heteroaryl groups include pyrrolyl, pyrazinyl, furyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thienopyridyl, pyrrolopyridyl, furanopyridyl, furazanyl, quinoxalinyl, quinazolinyl, quinolizinyl, imidazo[1,2-a]pyridyl, phthalazinyl, imidazo[2,1-b]thiazolyl, benzofuranyl, indolyl, isoindolyl, indolizinyl, indazolyl, azaindolyl, benzimidazolyl, benzothienyl, benzisoxazolyl,

benzothiazolyl, purinyl, benzotriazolyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, imidazolyl, isoquinolinyl, cinnolinyl, triazinyl, benzotriazinyl, and the like. Preferred heteroaryl group substituents include hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamyl, thiocarbamyl and amidino. When heteroaryl contains a nitrogen atom, the nitrogen atom may be oxidized to the N-oxide.

Hence, Ewing et al. teach the 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S with optional substitution.

Therefore, taking the teachings of Ewing et al. one of ordinary skill in the art could develop the following molecule:



which reads on the instant claims when B is cyclohexyl substituted at the 4 position with $(CRR)_rNR^{5a}R^{5a}$ with r being 0 and R^{5a} being alkyl substituted as defined; R^1 is phenyl; a is a single bond; R^{10} and R^{13} are H; n is 1; Z is -NH-; R^2 is a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted as defined; E, X, R^e, R^{11}, and all other substituents are as defined.

One of ordinary skill in the art would have been able to adapt the synthetic schemes (22 schemes were presented on pages 65-80) and the examples (880 examples were presented on pages 80-230) to make the compounds of the instant invention. The motivation to do so was provided by Ewing et al. in that the synthesized compounds are to be used to inhibit Factor Xa to treat disorders related to blood coagulation in mammals. See page 1, line 11 through page 2, line 7; and page 5, lines 2-4. The fact that the intended uses of the compounds is different (the treatment of diseases mediated by CCR2 in the instant application and the treatment of diseases mediated by factor Xa in Ewing et al.) is immaterial when considering a product claim in that the product is being claimed and not a method of using the product.

Claim 15 has been cancelled, which obviates the rejection of claim 15 under 35 U.S.C. 103(a) and the rejection of claim 15 is hereby withdrawn.

However, the arguments to the rejection of claims 1-14 and 16-19 under 35 U.S.C. 103(a) as being unpatentable over Ewing et al. were not found persuasive and the rejections still stand.

Previous Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

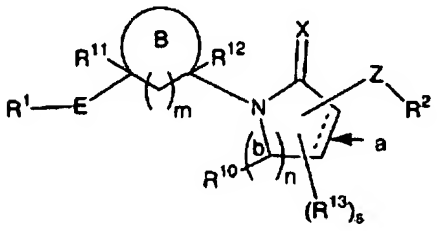
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

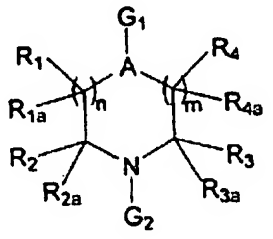
Claims 1-14 and 16-19 rejected under 35 U.S.C. 103(a) as being unpatentable over Ewing et al. (WO 99/37304 A1).

The instant application cites a compound of the base structure



where: B is cyclohexyl with substitutions as defined; a is a single bond; R^1 is phenyl with substitutions as defined; n is 1; Z is -NH-; R^2 is a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted as defined; E, R^1, R^{11}, and all other substituents are as defined.

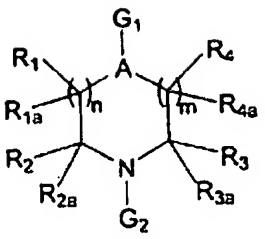
Determination of the scope and content of the prior art (MPEP §2141.01)

Ewing et al. teach a lactam with the base formula:  with substitutions as defined. See page 2, line 18.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Ewing et al. do not teach specifically the compounds of the instant invention.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Ewing et al. teach generally lactams with the base formula:  in which n is 0; R_2 and R_{2a} combine to make =O or =S; G_2 is L_2-Cy_2 where L_2 is absent and Cy_2 is optionally substituted cycloalkyl; A is CH; G_1 is L_1-Cy_1 where L_1 is NR^5 where R^5 is hydrogen and Cy^1 is optionally substituted heteroaryl; m is 1; R_3, R_{3a}, R_4, and R_{4a} are as defined.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to follow the synthetic scheme of Ewing et al. and make the claimed invention with a reasonable expectation of success. The motivation to do so is provided by Ewing et al. Ewing et al. teach the use of the synthesized compounds to inhibit Factor Xa to treat disorders related to blood coagulation in mammals. See page 1, line 11 through page 2, line 7; and page 5, lines 2-4.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

New Claim Rejections - 35 USC § 103

The following new rejection was necessitated by amendment as this is a new claim.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

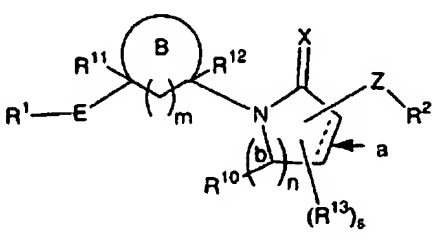
the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

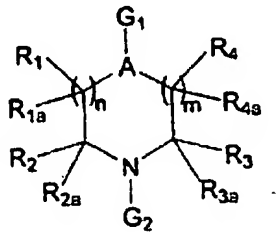
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 37 rejected under 35 U.S.C. 103(a) as being unpatentable over Ewing et al. (WO 99/37304 A1).

The instant application cites a composition containing a compound of the base structure  where: B is cyclohexyl with substitutions as

defined; a is a single bond; R^1 is phenyl with substitutions as defined; n is 1; Z is -NH-; R^2 is a 5-10 membered heteroaryl system containing 1-4 heteroatoms selected from N, O, and S, substituted as defined; E, R^1, R^{11}, and all other substituents are as defined.

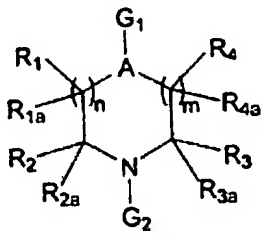
Determination of the scope and content of the prior art (MPEP §2141.01)

Ewing et al. teach a lactam with the base formula:  with substitutions as defined. See page 2, line 18. Ewing et al. also teach the pharmaceutical composition. See page 232, lines 23-25.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Ewing et al. do not teach specifically the compounds of the instant invention.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Ewing et al. teach generally lactams with the base formula:  in which n is 0; R_2 and R_{2a} combine to make =O or =S; G_2 is L_2-Cy_2 where L_2 is absent and Cy_2 is optionally substituted cycloalkyl; A is CH; G_1 is L_1-Cy_1 where L_1 is NR^5 where R^5 is hydrogen and Cy^1 is optionally substituted heteroaryl; m is 1; R_3, R_{3a}, R_4, and R_{4a} are as defined.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to follow the synthetic scheme of Ewing et al. and make the claimed invention with a reasonable expectation of success. The motivation to do so is provided by Ewing et al. Ewing et al. teach the use of the synthesized compounds to inhibit Factor Xa to treat disorders related to blood coagulation in mammals. See page 1, line 11 through page 2, line 7; and page 5, lines 2-4.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

Conclusion

Claims 1-14, 16-19, and 37 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Kosack whose telephone number is (571)-272-5575. The examiner can normally be reached on M-F 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph R Kosack

Joseph Kosack
Patent Examiner
Art Unit 1626

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

Kamal Saeed

Joseph K. McKane
Supervisory Patent Examiner
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